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Serum Immunoglobulins in the Differential Diagnosis Between Intrahepatic Viral Jaundice and Extrahepatic Obstructive Jaundice*

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Serum immunoglobulin levels are reported in 75 patients with jaundice; 32 with jaundice due to virus hepatitis and 43 with jaundice due to obstruction. The degrees and variations of serum immunoglobulins (Ig), (IgM, IgG and IgA) in virus hepatitis (IH and SH) with jaundice are compared with those found in obstructive jaundice. In 32 of the patients with jaundice from virus hepatitis, serum IgM (100%) and IgG (75%) were elevated above 2 Standard Deviations from the mean values. Neither IgM nor IgG levels were elevated above 2 Standard Deviations from the mean values in 33 of 43 patients (76.7%) with obstructive jaundice. In the other 10 patients, serum IgM (21%) and IgG (7%) were elevated above 2 Standard Deviations from the mean values. Case histories are presented of the five of nine patients, with obstructions and IgM elevations who had inflammatory reactions about the biliary tract.

The role of immunoglobulins in various liver conditions has not been reported to any great extent in the literature. The references that do exist are concerned mainly with alcoholic cirrhosis [2,3,4] except for Lee's data which compares the immunoglobulins in viral hepatitis and alcoholic liver disease.[3] Unfortunately, the measurements of serum immunoglobulins have not been universally standardized and no quantitative comparison can be made of the values found in different laboratories. A standard for normal serum immunoglobulins (Ig) (IgM, IgA and IgG†) has been established in this laboratory using a micro-double diffusion in agar slide technic. Using these values as a standard, Ig determinations were made on two groups of jaundiced patients: those found to have viral hepatitis and those with extrahepatic obstructions. The *degrees* and *variations* in *serum immunoglobulin* levels during the icteric stage of virus hepatitis have been reported in detail[5,6,7] and suggested the present clinical investigation. The elevated values of IgM associated with viral jaundice and the variable values for IgG and IgA during this period are stressed. In contrast, there was a lack of serum immunoglobulin elevation in the majority of patients with jaundice due to

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†Recommended terminology for the major immunoglobulins (Ig) classes: IgM (19S, beta-2 macroglobulin); IgA (7S, beta-2A globulin) and IgG (7S, gamma-2 globulin) (8).

extrahepatic obstructive conditions. The serum immunoglobulins are elevated in a relatively small percentage of obstructive conditions, usually when there is associated inflammation. Thus, immunoglobulin determinations were found to be a valuable aid in differentiating between intrahepatic virus hepatitis jaundice and extrahepatic obstructive jaundice.

Patient Source and Studies

The differentiation between intrahepatic virus jaundice and extrahepatic obstructive jaundice was made on the surgical service. No patients with a history of possible drug-induced jaundice are included in this report. The differential diagnosis of virus hepatitis was made on the clinical signs and symptoms, liver function tests, serum bilirubin values above 2.5 mg/100 ml, serum glutamic oxaloacetic transaminase (SGOT) levels and serum alkaline phosphatase levels. All obstructive cases in this report were verified by surgery. Serum immunoglobulin levels were determined along

Table I

SERUM PROTEINS, IMMUNOGLOBULINS (Ig), SGOT AND BILIRUBIN IN INFECTIOUS (IH) AND TRANSFUSION ASSOCIATED HEPATITIS (SH)

		ELECTROPHORESIS		IMMUNO-ANALYSIS			SERUM VALUES	
	AGE In Years	Beta (0.2-1.3) g%	Gamma (0.4-1.4) g%	IgG (0.6-1.4) g%	IgM (40-120) mg%	IgA (30-135) mg%	SGOT (5-40) u/ml	Bilirubin Total/Direct (0.02-1.0/0.05-0.3) mg%
	20	0.8	2.2 ▲*	2.0 ▲*	180 ▲	166 ▲	85	2.9/0.5
	20	1.0	2.7 ▲	1.9 ▲	208 ▲	57	56	2.24/0.94
	21	1.0	2.3 ▲	1.5 ▲	253 ▲	131	210	7.4/2.6
	23	0.6	2.0 ▲	2.4 ▲	1530 ▲	93	155	3.8/2.5
	25	0.7	1.5 ▲	1.8 ▲	221 ▲	85	155	10.4/5.1
	25	0.9	1.5 ▲	1.8 ▲	248 ▲	96	2200	2.5/0.96
	27	1.2	1.6 ▲	1.6 ▲	215 ▲	39	45 ±	6.2/---
	39	0.6	1.8 ▲	1.6 ▲	288 ▲	96	21	3.1/.32
IH	42	1.1	1.9 ▲	1.5 ▲	121 ▲	207 ▲	1060	9.60/5.45
	45	0.8	1.4 ▲	1.5 ▲	283 ▲	162 ▲	260	12.8/8.0
	52	0.8	0.9	1.5 ▲	228 ▲	218 ▲	1800	11.5/7.3
	63	1.2	1.5 ▲	1.9 ▲	320 ▲	260 ▲	90	3.8/2.0
	63	0.3	4.2 ▲	5.3 ▲	294 ▲	528 ▲	1300	7.7/4.1
	24	1.3	0.7	0.7	239 ▲	128	180	4.8/2.4
	25	0.8	1.3	1.1	184 ▲	69	6000	11.5/5.4
	31	0.6	1.1	1.3	176 ▲	25 ▼	300	3.1/1.35
	42	0.6	1.5 ▲	1.3	302 ▲	103	3100	5.5/2.9
	49	0.8	1.5 ▲	1.4	214 ▲	80	511	7.0/4.5
	35	0.3	3.9 ▲	2.9 ▲	293 ▲	130	900	10.5/5.7
	39	1.0	2.4 ▲	1.8 ▲	401 ▲	251 ▲	500	8.7/4.5
	44	0.8	1.8 ▲	1.5 ▲	150 ▲	170 ▲	1650	7.4/4.5
	44	0.5	3.1 ▲	2.8 ▲	217 ▲	192 ▲	2240	41/21
	45	0.8	0.7	1.7 ▲	1098 ▲	58	2200	13.1/7.0
SH	48	0.5	1.4 ▲	1.5 ▲	144 ▲	159 ▲	1840	11.9/4.8
	55	0.9	2.1 ▲	1.9 ▲	165 ▲	138 ▲	1600	3/1.6
	55	1.1	1.4	1.5 ▲	224 ▲	126	2000	14/6
	57	0.8	1.4	1.7 ▲	130 ▲	156 ▲	580	6.8/3.2
	60	1.0	1.6 ▲	2.2 ▲	384 ▲	278 ▲	3100	9.9/4.8
	46	0.6	1.4	1.2	176 ▲	130	1100	10.5/5.4
	60	0.4	1.4	1.2	204 ▲	175 ▲	3900	20.4/10.2
	72	0.7	1.2	1.0	152 ▲	101	410	32/7
	73	0.9	2.0 ▲	1.4	129 ▲	240 ▲	1550	15.68/9.28

* Arrows indicate values above (▲) or below (▼) 2 Standard Deviations from the mean.

with the indicated liver function tests. No flocculation tests were included since there was no correlation between these and the immunoglobulin values.

Serum bilirubin values are included in Table I for virus hepatitis patients only. Serum bilirubin values are omitted in the obstructive jaundice tables to simplify the tables, since all patients had clinical jaundice and the elevated values show no correlation with immunoglobulin responses. Serum glutamic oxaloacetic transaminase (SGOT) and alkaline phosphatase levels are included for comparative evaluation with the immunoglobulin levels. The percent protein distribution values for the *beta* and *gamma* zones of the electrophoretic mobility patterns are included in the tables in order to emphasize the limited information on serum immunoglobulin levels obtainable from this test. Electrophoretic mobility patterns do not show IgM and IgA values because these components are shadowed in the beta and gamma zones. Immunochemical analysis is necessary for the determination of these components.

Electrophoretic Mobility of Serum Proteins — The standard biuret procedure was used for determining total proteins. The standard method for serum electrophoresis on cellulose acetate strips was used to determine percent distribution of serum proteins.

Quantitative Determination of Serum Immunoglobulins (Ig) — Serum immunoglobulins (IgM, IgG and IgA) were determined by a micro-double diffusion in an agar slide technic developed and standardized in this laboratory.[9,10]

Normal adult serum immunoglobulin levels have been found to range (mean ±2 Standard Deviations*) as follows: 40-120 mg/100 ml (mean 79 mg) for IgM; 600-1400 mg/100 ml (mean 1004 mg) for IgG; and 30-135 mg/100 ml (mean 82 mg) for IgA.

Serum Transaminase and Alkaline Phosphatase — Serum glutamic oxaloacetic transaminase (SGOT, normal values 5-40 units/ml) and serum alkaline phosphatase (normal values 1.5-4.0 Bodansky units/100 ml) determinations were performed on fresh serum by the clinical biochemistry laboratory.

Results As Tabulated

Of 75 jaundiced patients studied, 32 were ultimately diagnosed as having viral hepatitis and 43 as having extrahepatic obstruction. Only single determinations are given for each patient, these representing the values found on first examination during the icteric stage.

Table I lists the virus hepatitis patients: with 18 IH patients and 14 SH patients grouped separately. Tables II, III, IV and V list the patients with obstructive jaundice. They have been grouped in an attempt to correlate the laboratory data with the respective obstructive conditions with jaundice: Table II showing 11 patients with choledocholithiasis; Table III showing 7 patients with cholecystitis and cholelithiasis; Table IV, 11 patients with carcinoma of the pancreas; and Table V, showing 14 patients with a variety of extrahepatic obstructive conditions. These tables show: (a) the *Beta* and *Gamma zone values* from electrophoretic mobility patterns of the

*The normal range of variations have been given the nearest convenient whole number for clinical usage.

Table II

SERUM PROTEINS, IMMUNOGLOBULINS (Ig) AND ENZYMES IN CHOLEDOCHOLITHIASIS WITH JAUNDICE

AGE	ELECTROPHORESIS		IMMUNO-ANALYSIS			ENZYMOLOGY	
	Beta (0.2-1.3) g%	Gamma (0.4-1.4) g%	IgG (0.6-1.4) g%	IgM (40-120) mg%	IgA (30-135) mg%	SGOT (5-40) u/ml	A-P'ase (1.5-4.0) u/100 ml
15	0.9	1.0	0.9	124 ↑	106	135 ↑	20 ↑
59	0.5	0.7	0.5 ↓*	30 ↓	88	165 ↑	36 ↑
65	0.9	0.8	0.8	56	72	62 ↑	19 ↑
68	1.2	1.1	0.9	83	165 ↑	100 ↑	9.3 ↑
69	0.5	0.7	0.9	94	95	---	2
77	0.6	1.0	0.8	103	94	40	13 ↑
42	0.9	1.0	1.1	83	153 ↑	210 ↑	32 ↑
63	0.8	0.5	0.7	50	154 ↑	40	18 ↑
82	0.8	0.7	0.9	62	255 ↑	17	19 ↑
75	1.0	1.7	1.74 ↑	75	152 ↑	220 ↑	7 ↑
81	---	---	2.34 ↑	139 ↑	227 ↑	55 ↑	6 ↑

* Arrows indicate values above (↑) or below (↓) normal range of variations.

Table III

SERUM PROTEINS, IMMUNOGLOBULINS (Ig) AND ENZYMES IN CHOLECYSTITIS AND CHOLELITHIASIS WITH JAUNDICE

AGE	ELECTROPHORESIS		IMMUNO-ANALYSIS			ENZYMOLOGY	
	Beta (0.2-1.3) g%	Gamma (0.4-1.4) g%	IgG (0.6-1.4) g%	IgM (40-120) mg%	IgA (30-135) mg%	SGOT (5-40) u/ml	A-P'ase (1.5-4.0) u/100 ml
56	0.7	1.1	0.9	55	61	220 ↑	4
62	0.7	0.8	0.5 ↓*	33 ↓	123	13	13 ↑
70	1.0	1.6 ↑	0.9	57	54	115 ↑	13 ↑
76	1.1	0.4	0.8	36 ±	120	195 ↑	12 ↑
73	1.0	1.0	0.7	71	248 ↑	25	5
83	0.7	0.9	0.9	72	212 ↑	73 ↑	5 ±
83	0.7	0.9	0.9	72	212 ↑	73 ↑	5 ±

* Arrows indicate values above (↑) or below (↓) normal range of variations.

serum protein distribution, which are compared with: (b) the *serum immunoglobulin* levels for IgM, IgG and IgA; and (c) the serum enzyme levels for serum glutamic oxaloacetic-transaminase (SGOT) and alkaline phosphatase (A-P'hase). The results are given in detail to emphasize the value of immunoglobulin levels in differentiating *inflammatory* from the non-inflammatory conditions in the jaundiced patient, a diagnosis which the other parameters do not reflect.

Serum Immunoglobulin (Ig) Levels in Virus Hepatitis (Table I) — Of the 32 viral hepatitis patients (ages 20 to 49 years), 18 were infectious (IH) and 14 with associated transfusion (SH). Elevated IgM was the most consistent finding in adults with virus hepatitis (SH and IH) during the acute stage of jaundice. This was shown in 32 of the patients (100%) listed in Table I in whom the serum levels for IgM were above 2-Standard Deviations (2-SD) from the mean. IgG elevations above 2-SD from the mean were found in 23 of these (75%*) (13 with IH and 10 with SH). All three immunoglobulins (IgM, IgG and IgA) were elevated in 13 (44%). The degrees and variations of Ig responses bear no apparent relationship to the severity of the disease. The infectious hepatitis patients, with low SGOT values on initial evaluation, demonstrated a rise in these levels as the disease progressed. However, the IgM levels in these patients were elevated at the initial determination. SGOT values in transfusion-associated hepatitis were found above 400 u/ml with the elevated IgM values.

Table IV

SERUM PROTEINS, IMMUNOGLOBULINS (Ig) AND ENZYMES IN CARCINOMA-PANCREAS WITH JAUNDICE

AGE	ELECTROPHORESIS		IMMUNO-ANALYSIS			ENZYMOLOGY	
	Beta (0.2-1.3) g%	Gamma (0.4-1.4) g%	IgG (0.6-1.4) g%	IgM (40-120) mg%	IgA (30-135) mg%	SGOT (5-40) u/ml	A-P'ase (1.5-4.0) u/100 ml
46	1.0	1.2	1.0	162 ↑*	56	180 ↑	18 ↑
57	0.8	1.4	0.9	83	61	35	17 ↑
63	0.8	0.6	0.9	96	127	800 ↑	23 ↑
67	0.9	0.4	0.6	105	136 ±	10	31 ↑
73	0.7	0.9	1.1	118	84	255 ↑	31 ↑
51	0.9	0.9	1.1	84	138 ±	21	18 ↑
52	1.0	1.1	1.1	57	161 ↑	38	27 ↑
61	1.0	0.8	1.0	108	233 ↑	110 ↑	13 ↑
66	1.5 ↑	0.9	1.2	56	229 ↑	20	8 ↓
78	0.9	0.9	1.1	62	204 ↑	55 ↑	8 ↓
54	0.8	1.1	1.2	142 ↑	172 ↑	45 ↑	11 ↑

* Arrows indicate values above (↑) or below (↓) normal range of variations.

*All percentages expressed in the nearest whole number.

Serum Immunoglobulin Levels in Extrahepatic Obstructive Jaundice. (Tables II, III, IV and V). In obstructive jaundice, IgM levels were within normal range of variation in 33 of 43 patients (77%). No interpretation can be given to the significance of IgA variability at this time with our data. The data in Table II are given separately because these patients had choledocholithiasis. In Table III the patients had evidence of cholecystitis without choledocholithiasis or any other obstruction to the common bile duct. The data given on 43 jaundiced patients (ages 15 to 83 years), with final diagnoses of extrahepatic obstructive jaundice showed the following results (Table VI): Nine patients (21%) had elevated IgM levels; seven, only IgM elevations, and two, both IgM and IgG elevations. Only one patient (2%) showed an elevated IgG level. Serum IgG levels were within normal range of variation in 40 of 43 patients (93%) with obstructive jaundice (Table VI). IgA appeared to be of little value in the differentiation: 21 of the 43 patients (51%) with obstruction showed values above normal.

Lack of Correlation Between Serum Immunoglobulin Levels and Serum Protein Distribution in Electrophoretic Mobility Values. In comparing electrophoretic mobility values for the five zones in the pattern, the beta and gamma zones are not reliable values for the elevated immunoglobulin components, even though they contribute to these mobility zones. The IgG value by immunochemical analysis is not always

Table V

SERUM PROTEINS, IMMUNOGLOBULINS (Ig) AND ENZYMES IN MISCELLANEOUS OBSTRUCTIONS WITH JAUNDICE

PT. NO.	AGE IN YEARS	DIAGNOSIS	ELECTROPHORESIS Beta (0.2-1.3) g%	Gamma (0.4-1.4) g%	IMMUNO-ANALYSIS IgG (0.6-1.4) g%	IgM (40-120) mg%	IgA (30-135) mg%	ENZYMOLOGY SGOT (5-40) u/ml	A'Phase (1.5-4.0) u/100 ml
	79	Ca - Gall B.	1.0	1.4	1.3	45	150↓	41	----
	81	Ca - Gall B.	1.0	1.8↑*	0.9	48	271↑	51 ±	19↑
	71	Ca - Gall B.	---	---	0.9	97	128	30	55↑
GS-35	79	Ca - Gall B.	0.8	2.09↑	0.8	160↑	178↑	----	10↑
	67	Ac. pancreatitis	0.6	1.9↑	1.1	89	177↑	43	21↑
	26	Ac. pancreatitis	----	----	2.3↑	139↑	23↓	----	4
GS-61	58	Ac. pancreatitis	0.8	1.3	1.2	154↑	128	145↑	18↑
	49	Chr. pancreatitis	1.2	0.6	1.2	62	163↑	40	73↑
	31	Chr. pancreatitis	0.8	1.4	1.4	71	146↑	----	46↑
GS-60	27	Stenosis - CBD	0.8	0.9	0.7	336↑	88	35	32↑
	42	Stenosis - CBD	----	----	1.0	59	97	----	11↑
GS-3	59	Obstr. - Prox. Bile Ducts	1.2	0.9	0.9	170↑	208↑	41	14↑
	72	Obstr. - Prox. Bile Ducts	0.8	1.4	1.2	51	200↑	145↑	11↑
GS-40	44	Neoplasm Bile Duct	1.0	1.0	0.9	224↑	72	73↑	44↑

* Arrows indicate values above (↑) or below (↓) normal range of variations

comparable to the gamma zone in electrophoresis. With few exceptions, the values for the two methods vary in all the tables for both virus hepatitis and obstructive jaundice patients. In addition, the values in the gamma zone by electrophoresis may show hypo-gamma or hyper-gamma values which are actually misleading.

Immunoglobulin-M Elevation Without Immunoglobulin-G Elevation in Patients with Jaundice. Of the 43 patients with obstructive jaundice, 16 showed normal serum values for all three immunoglobulins (IgM, IgG and IgA) and 33 showed normal serum values for IgM and IgG. However, IgM was elevated in nine patients of whom seven had normal IgG values and two had elevated IgG values. These responses are in marked contrast to those seen in infectious hepatitis patients where IgM (100%) with IgG (75%) are more consistently elevated during the icteric stage of the disease. A delay in the rise of IgG during the icteric stage is seen in virus hepatitis.[5,6,7] For this reason, patients with an initial elevation of IgM alone are studied weekly for the possible elevation of the IgG component. With few exceptions, obstructive jaundice with inflammation is probable when IgM is elevated without IgG elevation; a nidus of gram-negative bacterial infection possibly stimulating the IgM response.

The contrast between the two responses is clearly shown in Table VI summarizing the IgM and IgG responses of the 75 patients in this report. It shows 32 having viral hepatitis with jaundice and 43 obstructive jaundice. Since IgA elevations bear little signifiicance in the differentiation between either virus hepatitis or obstructive

Table VI

SUMMARY OF IMMUNOGLOBULINS (IgM and IgG) IN 75 JAUNDICE PATIENTS

Clinical Entity	Total Patients	Serum Ig's Normal	Number of Patients with Immunoglobulins Affected Above Normal Serum Levels (▲)*		
			IgG ▲	IgM ▲	IgG ▲ IgM ▲
Choledocholithiasis	11	9	1	0	1
Cholecystitis and Cholelithiasis	7	7	0	0	0
Ca - Pancreas	11	9	0	2	0
Ca - Gallbladder	4	3	0	1	0
Chr. pancreatitis	2	2	0	0	0
Ac. pancreatitis	3	1	0	1	1
Stenosis CBD	2	1	0	1	0
Neoplasms of prox. biliary duct	3	1	0	2	0
Total Obstructions:	43	33 (76.7%)	1 (2.3%)	7 (16.3%)	2 (4.6%)
Total Virus Hepatitis	32	0	0	32 (100%)	23 (75%)

* Serum levels above 2SD from mean.

jaundice and as it is little understood at present, these values have been omitted. However, IgA has been reported in relation to its significance in cirrhosis in alcoholism.[2,3,4] What relation IgA has to other types of chronic liver diseases is yet to be determined.

Five Case Histories with IgM Elevations in Obstructive Jaundice. Five of the seven patients with IgM elevations without IgG elevations are reviewed below. All warranted surgical intervention after observation and medical management. Four of the seven patients (Table V) were found to have bile duct obstructions (GS-3, GS-35, GS-40 and GS-60). The remaining patients with IgM elevations had acute or chronic pancreatitis (viz. GS-61).

Patient GS-3 (Table V), was a 59-year-old white man with jaundice of two weeks' duration. Epigastric pain had begun two weeks prior to jaundice and was followed by nausea and dark urine one week later. Physical examination on admission to Henry Ford Hospital (July 31, 1965) was essentially negative except for jaundice, permanent tracheotomy and a left thoracotomy surgical scar. (Laryngectomy and permanent tracheotomy for carcinoma of the larynx had been performed in 1957 and a lobectomy for adeno-carcinoma in 1964). Laboratory findings on admission were: total bilirubin 14 mg/100 ml and direct bilirubin 8 mg/100 ml; SGOT 41 units; alkaline phosphatase 14.7 Bodansky units; prothrombin time 15 seconds (control 15 seconds); hemoglobin 10.9 gm/100 ml; WBC 5,300 with a normal differential. Serum IgM (170 mg/100 ml) and IgA (208 mg/100 ml) were elevated above 2-SD from the mean, while IgG (855 mg/100 ml) was within normal range of variation. These values were more suggestive of obstructive jaundice than viral hepatitis. The serum enzyme levels were also suggestive of obstruction necessitating surgical intervention. This was performed 8-10-65. The common duct was explored and an operative cholangiogram showed an obstruction of the common hepatic duct. As the obstruction was within the hepatic substance, decompression of the biliary tree could not be accomplished. The liver biopsy showed cholestasis. Serum immunoglobulin values for IgM (149 mg/100 ml) and IgA (167 mg/100 ml) remained elevated after surgery, as would be expected, since the obstruction was not relieved. When the patient expired on 9-7-65, permission for an autopsy was not obtained.

Patient GS-35 (Table V), a 79-year-old white woman, was seen on 2-26-66 with jaundice of two to three weeks duration, right upper quadrant tenderness and an enlarged liver. Laparotomy had been performed at this hospital on 8-26-65 for possible gallstone ileus. No obstruction was found, but a large inflammatory mass was noted in the right upper quadrant. It was felt that the patient had passed her gallstones and no definitive surgery was performed. Laboratory findings for the 2-26-66 admission were: total bilirubin 2.56 mg/100 ml; direct bilirubin 1.28 mg/100 ml; alkaline phosphatase 10.7 Bodansky units; serum amylase 68 units; fasting blood sugar 100 mg/100 ml; blood urea nitrogen 11 mg/100 ml and prothrombin time 15 seconds (control 12 seconds); hemoglobin 10.8 gm/100 ml and WBC 11,200 with a shift to the left. Serum immunoglobulin levels on 3-1-66 were elevated for IgM (160 mg/100 ml) and for IgA (178 mg/100 ml) whereas IgG (839 mg/100 ml)

was within the normal range of variation. Pre-operative immunoglobulin values and duration of illness were more suggestive of obstruction. The operative diagnosis was carcinoma of the gallbladder with cholecystoduodenal fistula and choledocholithiasis. The operative procedure consisted of: (1) excision of the fistula with closure of the duodenum; (2) exploration of the common bile duct with removal of the stone; and (3) anterior gastrojejunostomy. Post-operative immunoglobulin values (3-25-66) showed the IgM (86 mg/100 ml) had returned to normal, possibly as a result of removal of the common duct obstruction and local inflammation. However, the malignant condition was not significantly improved, which could account for the persistent IgA elevation. In addition, the increase in IgG value from 839 mg/100 ml to 1,392 mg/100 ml could be explained by the development of a post-operative infection.

Patient GS-40 (Table V), a 44-year-old white woman, was seen on 4-9-66 with jaundice and a large, smooth, non-tender liver. She had previously had episodes of epigastric pain without jaundice in 1962, and with jaundice in April, 1965. An episode of jaundice in December, 1965, accompanied by nausea and acoholic stools led to surgical intervention at another hospital on 2-2-66. An operative cholangiogram showed an obstruction of the proximal common bile duct with dilation of the left hepatic duct. A cholecystectomy and left hepatoduodenostomy was performed. The patient failed to improve and was referred to Henry Ford Hospital on 4-9-66. Laboratory findings at this time were: total bilirubin 13.4 mg/100 ml; direct bilirubin 8 mg/100 ml; SGOT 73 units; alkaline phosphatase 43.5 Bodansky units; serum amylase 98 units; prothrombin time 17 seconds (normal 12 seconds); hemoglobin 11.0 gm/100 ml; WBC 8,550 with a normal differential; and 24-hour urinary amylase 2,883 units per total volume. Serum immunoglobulin values on 4-20-66 showed elevated IgM (224 mg/100 ml) levels but normal IgA (72 mg/100 ml) and IgG (896 mg/100 ml) values. There was a posibility of viral hepatitis or persistent obstruction. Since IgG and IgA values were normal, IgM elevation together with the serum enzyme values were more indicative of obstruction rather than viral hepatitis. The operative findings indicated the probable presence of a neoplasm of the common bile duct but this diagnosis was not substantiated by biopsies which showed reactive hyperplasia and chronic inflammation. Surgical procedure on 4-21-66 was: (a) left hepatojejunostomy; (b) biopsy of liver and lymph node; and (c) operative cholangiogram. Post-operative IgM value (93 mg/100 ml) returned to normal (4-28-66) and IgG with IgA decreased in serum levels to 42 mg/100 ml and 562 mg/100 ml respectively. The patient recovered and was discharged 10 days post-operatively.

Patient GS-60 (Table V), a 27-year-old white woman, was seen on 10-30-66 with nausea and jaundice. This occurred 9 months following surgery for a complete transection of the common bile duct incurred as a result of an automobile accident. An end-to-end anastomosis had been performed (1-5-66). Laboratory studies on admission (10-30-66) were: total bilirubin 5.8 mg/100 ml; direct bilirubin 3.5 mg/100 ml; SGOT 35 units; alkaline phosphatase 32 Bodansky units; serum amylase 28 units; prothrombin time 13 sec. (control 12 sec.); 24-hour urinary amylase 3,400 units/volume; hemoglobin 14.8 mg/100 ml; and WBC 9,200 with a normal differ-

ential. Serum immunoglobulin-M (336 mg/100 ml) was elevated above 2-SD from the mean, while IgG (745 mg/100 ml) and IgA (88 mg/100 ml) were within the normal range of variation. The elevated IgM together with the history and serum enzyme values suggested an obstructive jaundice rather than infectious hepatitis. Operative finding on 11-4-66 was common bile duct stricture at the anastomotic site. The operative procedure was Roux-Y choledochojejunostomy and liver biopsy. The liver biopsy showed "subacute inflammation in portal triads."

Patient GS-61 (Table V), a 58-year-old woman, presented with epigastric pain, nausea and low grade fever of two weeks' duration before jaundice appeared (11-14-66). Past history revealed that cholecystostomy had been performed in September of 1962 for an acute gangrenous cholecystitis and a cholecystectomy performed in April, 1963. Laboratory findings on admission (11-14-66) were: total bilirubin 4.2 mg/100 ml; direct bilirubin 1.9 mg/100 ml; SGOT 145 units; alkaline phosphatase 17.9 Bodansky units; serum amylase 768 units; LDH 370 units; prothrombin time 15 sec. (control 12 sec.); 24-hour urinary amylase 16,200 units/volume; hemoglobin 11.5 gm/100 ml and WBC 10,600 with a shift to the left. Serum immunoglobulin-M (154 mg/100 ml) was elevated above 2-SD from the mean while IgG (1,182 mg/100 ml) and IgA (128 mg/100 ml were within the normal range of variation. Although the serum enzymology was indicative of pancreatitis, the history of cholecystectomy for cholelithiasis warranted exploration of the common bile duct. Since IgM (154 mg/100 ml) elevation also suggested infection, medical therapy was instituted for 11 days, until serum enzyme values approximated normal levels, before surgery was performed. The operative findings were consistent with the diagnosis of chronic pancreatitis with no evidence of obstruction. Operative procedure was: (1) exploration of the common bile duct; (2) dilatation of the Sphincter of Oddi and (3) multiple biopsies. The liver biopsy showed "slight foci of chronic inflammation." Unfortunately, follow-up determinations on the immunoglobulins were not obtainable.

Serum Transaminase and Alkaline Phosphatase Values in Virus Hepatitis and Extrahepatic Obstructive Jaundice. No correlation could be seen between the *degrees of variations in immunoglobulin responses* and the serum enzyme values. They each reflect different biologic activity and pathologic physiology. The serum immunoglobulin levels are in response to antigenic stimulation to the lymphoreticular system whereas the serum enzyme levels are accumulation products from variable sources. It is of interest to note that SGOT values are more often seen above 400 u/ml of serum for transfusion-associated viral hepatitis than with infectious viral hepatitis during the acute icteric stage.

Discussion

Immunoglobulin (Ig) determinations in jaundiced patients reflect the humoral immune status of the individual. The significance of the serum immunoglobulin levels in the jaundiced patient are evaluated on the basis of the response of each immunoglobulin and also the combined responses of all three immunoglobulins. Moreover, the serum levels in this report are evaluated on whether each component approximates

the *mean values* or whether they are *above 2-SD from the mean.* Since the details of the immunoglobulin determinations are not given in this paper, it should be emphasized that each immunoglobulin value reported is an average value from 6 to 8 determinations (4 determinations are measured on each of two slide preparations, the routine procedure with the technic used). Thus, the values given for the immunoglobulins are highly significant when they are greater than 2-SD and 3-SD from the normal mean.

The 32 viral hepatitis patients in this report show results similar to the *degrees* and *variations* in published immunoglobulin responses in viral hepatitis (IH and SH) in children[5,6] and in adults.[7] Serum IgM values are elevated above 2-SD from the mean in virus hepatitis during the acute icteric stage in 90-100% of the patients whereas serum IgG may be concomitantly elevated in 70-90% of the patients. In contrast, elevations in IgM with IgG were found in only 4.6% of jaundiced patients with extrahepatic obstruction. In the remaining 95.4% of the patients with obstructive jaundice, only 17% showed elevated serum IgM values above 2-SD from the mean. This suggests obstruction with the complication of inflammation, as IgM elevation without IgG elevation has been found in common bile duct obstruction with inflammatory reactions in contiguous tissue. The nature of of the IgM response in obstruction is under investigation with more elaborate studies than are herein reported. Whatever the mechanism for inducing IgM elevation without IgG response, the stimulus is often removed when the obstruction is relieved. The IgM response might be explained on retrograde infection of the common bile duct with gram-negative bacteria.[11,12] Studies have also been reported in which specific antibody activity to a variety of micropathogens is associated with IgM component.[13,14] However, intrahepatic cholestasis (Patient GS-3) and pancreatitis (Patient GS-61) have also induced the same response as common bile duct obstructions (IgM elevation with normal IgG values). Although isolation studies were not made in this study, histopathology has shown inflammatory reactions to contiguous tissue. Immunologically, IgM elevation in a jaundiced patient indicates an inflammatory process and warrants a reasonable period of medical management and observation before surgical exploration. These guidelines are not found among the usual liver function tests in present use.

Since the more commonly used serum turbidity and flocculation tests employed to demonstrate liver disease have been based upon the gamma immunoglobulin studies by electrophoretic analysis and lipoprotein [15,16] content of the serum, it is more meaningful to measure these components directly for practical diagnostic significance. The controversies over the clinical significance of the turbidity and flocculation reactions[17,18] are understandable when one considers the degrees and variations found in the respective immunoglobulin components in viral hepatitis[3,5,6,7] and obstructive conditions producing jaundice. Parenthetically, the flocculation tests have not been done at this hospital for some time.

Evaluation of serum immunoglobulin components before and after surgery has offered an excellent means of differentiating post-transfusion hepatitis which follows administration of blood and blood products (IgM and IgG elevations, with IgA being variable) from persistent obstructive jaundice with or without inflammatory

response. As with any laboratory test, clinical findings and experience are required for interpretation and proper utilization of the results. The data presented emphasize the value of determining specific serum immunoglobulin components as another parameter in the evaluation of the jaundiced patient.

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