Serum Lactic Dehydrogenase, Leucine Aminopeptidase and 5-Nucleotidase Activities:

Observations in Patients with Carcinoma of the Pancreas and Hepatobiliary Disease

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ABSTRACT

Serum lactic dehydrogenase, leucine aminopeptidase, 5-nucleotidase and alkaline phosphatase activities were investigated in a number of diseases involving the hepatobiliary system.

Leucine aminopeptidase was found to be a sensitive indicator of biliary obstruction, serum 5-nucleotidase slightly less sensitive, and alkaline phosphatase appreciably less sensitive. Leucine aminopeptidase and 5-nucleotidase activities were often increased by malignant infiltration of the liver and primary hepatic disease even in the absence of jaundice.

Serum lactic dehydrogenase was frequently increased in primary hepatic disease and malignant disorders but was not apparently affected by bile duct obstruction *per se*. Thirty-five of 45 patients with proved malignancy had increased lactic dehydrogenase levels.

The highest leucine aminopeptidase levels were encountered in carcinoma of the head of the pancreas. The frequent increase in both serum lactic dehydrogenase and leucine aminopeptidase activities in patients with carcinoma of the head of the pancreas suggests that these combined estimations are useful laboratory procedures in the diagnosis of malignant extrahepatic obstruction.

MANY serum enzymes have been studied in relation to malignant neoplasia. Some of those which have received recent clinical attention include acid and alkaline phosphatase, lactic dehydrogenase, phosphohexoisomerase, leucine aminopeptidase, aldolase and ribonuclease. None of the enzymes studied is completely reliable for the diagnostic appraisal of malignant conditions, and all serum enzymes studied to date are known to be influenced by conditions other than malignancy.

We have investigated alterations in serum lactic dehydrogenase, leucine aminopeptidase and 5-nucleotidase in patients with a number of pathological states, and this report is concerned with the altered serum values encountered in pancreatic and hepatobiliary disease with particular reference to the diagnostic value of combined lactic dehydrogenase (LDH) and leucine aminopeptidase (LAP) estimations in the diagnosis of carcinoma of the pancreas.

Lactic dehydrogenase activity is known to be elevated in conditions associated with muscle and hepatic necrosis, but it has also been shown that such necrosis is not necessary for the passage of this enzyme from the intracellular to the extracellular environment.[1] It has been established in experiments with transplantable tumours that good correlation exists between increasing lactic dehydrogenase values and growth of the tumour,[2] and elevated serum levels are frequently encountered clinically in subjects with various malignant states.[3] The value of leucine aminopeptidase estimations remains controversial. This enzyme is known to be affected by biliary obstruction, but serum LAP levels may also be elevated in the presence of hepatic disease.[4] Some comparisons with serum alkaline phosphatase and 5-nucleotidase are included for comparative purposes. The latter enzyme is a specific form of phosphatase which is affected only in hepatobiliary diseases.[5, 6]

MATERIALS AND METHODS

Enzyme estimations were carried out on nonhemolyzed serum or plasma. Determinations were made either on fresh material or on specimens preserved by freezing. No significant alterations in enzyme activity were noted following 14 days' storage in the frozen state.

Lactic dehydrogenase activity was determined by a modification of Wroblewski's colorimetric procedure,[7] using incubation at 37° C. for 30 minutes at a pH of 7.2. The observed range for a group of normals was 120 to 305 units per 100 ml., with a mean value of 170.7 units.

Leucine aminopeptidase activity was determined by the method of Goldbarg and Rutenburg.[8] Our observed normal range was 80 to 230 units per 100 ml. with a mean of 136 units.

5-Nucleotidase activity was determined by using an adenosine-5-phosphate substrate at a pH of 7.3

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TABLE I.—SERUM ENZYMES IN CARCINOMA OF THE HEAD OF THE PANCREAS

	Bilirubin (mg.%)	*Enzymes (units/100 ml.)*				
		Alk. P'tase	*A-5-P*	*LDH*	*LAP*	
Normal range.....	*0-1*	*5.6-10.8*	*0.4-1.2*	*120-305*	*80-230*	*Remarks*
Case						
C.Ma.	18.8	12.4	1.8	456	360	Pancreatectomy
P.	19.3			204	1286	Gland metastases only
A.Fa.	57.0	19.0	2.8	625	588	" " "
C.Mo.	18.0			818	882	" " "
U.M.	14.8	10.8	5.8	450	1124	" " "
J.P.		24.8	4.8	564	1300	" " "
R.		19.6	7.4	857	1493	" " "
C.N.	1.0	21.5	5.0	197	1360	No metastases, previous bypass operation
S.B.	5.1	25.0	3.6	503	1837	Gland metastases, bypass operation
M.P.	19.3	14.8	7.4	495	867	Gland metastases
D.J.	2.3	24.0	16.2	1010	1558	Pancreatectomy
M.M.	7.4			412	1543	Gland metastases
D.C.	16.2			441	1720	
T.Su.	8.0			646	633	Bypass
I.H.	7.0			785	573	No metastases
J.H.	17.0			320	1411	Gland metastases, bypass and biliary cirrhosis
W.T.			1.9	169	963	Jaundice, liver metastases
S.C.	35.0			550	522	No metastases
E.Ch.	19.1	17.3	3.7	540	1029	Gland metastases
E.Ch.	2.0	10.5	1.3	785	588	Four weeks postoperative
T.Sa.	10.2			774	543	Gland metastases, bypass
T.Sa.	8.5			637	1492	Eleven weeks postoperative
A.Fo.	25.0	21.0	8.7	485	1143	Gland metastases, bypass
A.Fo.		21.0	4.2	450	241	Six weeks postoperative
C.S.	7.2	14.6	4.2	92	492	Gland metastases
C.S.	21.7			124	639	Two weeks later
H.A.	13.3			195	1323	Pancreatectomy
H.A.	3.3			185	1239	Three weeks postoperative
J.D.	31.0			135	757	Gland metastases, bypass
J.D.	0.8			460	147	Three weeks postoperative
L.S.	12.8			365	808	Pancreatectomy
L.S.				310	419	One month postoperative
L.S.					61	Seven weeks postoperative

Alk. P'tase = Alkaline phosphatase. LDH = Lactic dehydrogenase.
A-5-P = 5-nucleotidase. LAP = Leucine aminopeptidase.

and determining the phosphorus liberated after a one-hour incubation period. The results are expressed as units of activity, one unit being equivalent to 1 mg. of phosphorus. Normal levels were found to range from 0.4 to 1.2 per 100 ml. with a mean value of .85 units.

Alkaline phosphatase estimations were carried out using a B-glycerophosphate substrate at a pH of 9.5 and a one-hour incubation period. The expression of units was the same as that for 5-nucleotidase. Normal values were found to range from 5.6 to 10.8 per 100 ml. with a mean value of 8.3 units.

The diagnosis of all cases of malignancy was established by operation or autopsy and confirmed by microscopic examination of tissues. The diagnosis of non-malignant conditions was established by the usual clinical criteria and in some instances also by laparotomy and punch biopsy of the liver.

RESULTS

Carcinoma of the Head of the Pancreas

The results for serum bilirubin determinations and the various enzyme estimations for a group of patients with cancer of the head of the pancreas are shown in Table I. All patients in this group had jaundice at the time of the initial estimation, with one exception (CN). This patient had previously had a bypass operation elsewhere and was referred for pancreatectomy. It is noteworthy in this group that all enzyme estimations, with the exception of the LDH, were significantly elevated in every instance. The diagnosis of all cases in this group was established at operation by histological examination of tissue. It can be readily seen that although the serum bilirubin and serum LAP were both elevated, there is no correlation between the degree of hyperbilirubinemia and the increased serum LAP activity. LAP levels prior to any surgical intervention were abnormal in every instance and ranged from 360 to 1837 units, with a mean of 1008. The alkaline phosphatase and 5-nucleotidase activities were increased to some degree in every instance in which these estimations were carried out. 5-Nucleotidase values showed much greater proportional increases over the normal than alkaline phosphatase values, levels ranging from 1.8 to 16.2 units prior to operation, with a mean value of 5.5. Calculation of the coefficient of correlation for the 5-nucleotidase and LAP activities indicated negligible correlation between the activity of these enzymes ($P = 0.047$). In contrast to the constant abnormalities noted in the above-mentioned enzymes, a number of normal LDH values were encountered. Levels ranged from 92 to 1010 units

and the mean value for the group was 487. Twenty patients showed elevated levels, two of the patients showing higher levels three and four weeks following bypass operations even though obstruction was absent, as evidenced by the decreased serum bilirubin and alkaline phosphatase. Four of the seven patients with no metastases at operation had normal LDH values. Repeat estimations in six patients after pancreatectomy or procedures for the relief of obstruction revealed decreased LAP values in all but one; in the latter case (TSa) there had been a recurrence of jaundice. The LAP fell to normal in two instances. Four of the patients had elevated LDH values before surgery and two showed some lowering subsequently.

Carcinoma of the Body and Tail of the Pancreas

Serum enzyme levels for a series of patients with malignancy of the body and tail of the pancreas are shown in Table II. Only two of this group had clinical jaundice (J.S. and J.B.) and all but three had metastases in the liver. Two of the latter had normal LAP levels. Ten of the 16 patients studied showed elevated LAP values and 12 showed elevated LDH activity; two of these elevations occurred in non-icteric cases with no evidence of metastases at operation. It is to be noted that in some instances only one of the enzyme levels was increased while in others both LDH and LAP were increased. LDH levels ranged from 38 to 940 with a mean value of 417, and LAP activity ranged from 103 to 1411 with a mean value of 478 units. The serum alkaline phosphatase and 5-nucleotidase levels in this group are too few for comparison with the measurements of the other enzymes.

TABLE II.—SERUM ENZYMES IN CARCINOMA OF THE BODY AND TAIL OF THE PANCREAS

	Enzymes (units/100 ml.)				
Case	*Alk. P'tase*	*A-5-P*	*LDH*	*LAP*	*Remarks*
F.			405	307	Liver metastases
J.W.	19.4	2.0	275	360	" "
H.	20.0	2.7	555	103	" "
P.B.	9.8	0.9	595	201	" "
R.L.	19.7	2.7	940	911	" "
W.			308	147	" "
P.			384	172	" "
M.			506	647	" "
F.D.			575	118	Pancreatectomy
S.He.	13.5		403	338	Liver metastases
L.L.	22.7	0.9	485	360	" "
S.Ho.			344	497	No metastases
J.S.			755	1146	Glands and liver metastases, jaundice and carcinoid syndrome
J.B.		1.4	177	617	Bypass, porta glands and liver metastases
W.D.			38	125	No metastases
M.K.			303	1411	Liver metastases

Alk. P'tase = Alkaline phosphatase.
A-5-P = 5-nucleotidase.
LDH = Lactic dehydrogenase.
LAP = Leucine aminopeptidase.

Obstructive Jaundice from Bile Duct Calculi

The results for a group of patients with jaundice due to common bile duct obstruction by calculi are shown in Table III. LAP levels were elevated in all but one instance, enzyme activity ranging from 148 to 1176. LDH activity was elevated in only four instances and these increases were noted in cases complicated clinically by cholangitis. The alkaline phosphatase and the 5-nucleotidase activities in the instances estimated showed variable elevations; however in two cases normal 5-nucleotidase levels were encountered. The degree of elevation of these enzymes did not correlate with the observed serum LAP abnormalities.

TABLE III.—SERUM ENZYMES IN OBSTRUCTIVE JAUNDICE FROM CALCULI

	Enzymes (units/100 ml.)				
Case	*Alk. P'tase*	*A-5-P*	*LDH*	*LAP*	*Remarks*
W.B.		2.0	231	368	
R.W.	20.4	3.9	92	1110	
M.D.	19.6	1.2	125	148	
C.C.	22.0	1.2	210	691	
D.D.L.			97	1022	
F.L.	16.2		560	537	Cholangitis
C.O.	26.4	7.2	301	691	Cholangitis
S.L.			124	919	First estimation
S.L.	33.2		730	772	Second estimation, six-day follow-up, cholangitis
M.R.			545	559	First estimation, cholangitis
M.R.	19.7	3.1	250	735	Second estimation, five-week follow-up, recurrence of jaundice
F.B.	23.6	4.8	800	1176	First estimation, cholangitis
F.B.			198	441	Second estimation, six-day post cholecystectomy

Alk. P'tase = Alkaline phosphatase.
LDH = Lactic dehydrogenase.
A-5-P = 5-nucleotidase.
LAP = Leucine aminopeptidase.

TABLE IV.—SERUM ENZYMES IN PANCREATITIS

	Enzymes (units/100 ml.)				
Case	*Alk. P'tase*	*A-5-P*	*LDH*	*LAP*	*Remarks*
L.R.	5.7	2.1	515	162	Jaundice
G.	10.2	4.4	300	117	No jaundice
N.	7.4	1.0	69	139	" "
R.			425	124	" "
C.			498	228	" "
M.			510	615	" "
K.			150	500	" "
M.K.	12.4	3.8	296	161	" "
D.Y.	13.6	4.7	250	246	" "
B.	14.9	0.9	142	272	" "

Alk. P'tase = Alkaline phosphatase.
A-5-P = 5-nucleotidase.
LDH = Lactic dehydrogenase.
LAP = Leucine aminopeptidase.

Acute Pancreatitis

Serum LDH and LAP activities in 10 cases of acute pancreatitis are shown in Table IV. Slight jaundice was present in one patient only. The diagnosis in this group was established on clinical grounds and confirmed by serum amylase activity in excess of 300 Somogyi units. LAP activity was increased in four cases; values for the group ranged from 117 to 615, with a mean value of 256 units. The LDH activity varied from 69 to 515, with a mean level of 317 units. In only one instance were both LDH and LAP levels increased. The phosphatases showed variable elevations in a few instances but these alterations did not correlate with LAP activity.

Acute Hepatitis

Enzymatic activity of the serum in a group of patients with acute infectious hepatitis is shown in Table V. Most of the patients showed glutamic pyruvic transaminase levels in excess of 300 units. All of the enzymes studied showed variable in-

TABLE V.—SERUM ENZYMES IN ACUTE HEPATITIS

Case	Enzymes (units/100 ml.) Alk. P'tase	A-5-P	LDH	LAP	Remarks
J.M.			381	132	
O.			389	132	
H.	18.9	5.1	490	246	
R.			508	209	
Ma.			702	236	
B.	13.1	1.6	590	1257	
Mc.	17.9	1.7	540	764	
Ph.	16.0	4.4	132	205	
L.	19.0	2.2	550	882	
Pa.			286	298	
M.P.			440	382	
C.S.			650	287	
K.K.			353	339	
P.H.			233	674	
G.S.			675	544	
Mc.	13.2	8.5	382	138	
G.R.			456	206	
W.B.			382	306	
E.K.			457	316	
H.A.	12.0	2.6	270	309	First estimation
H.A.	0.2	0.2	403	132	Eight days follow-up
Q.C.	2.7	0.5	430	154	First estimation
Q.C.		0.2	178		1½-month follow-up
A.C.	11.2	2.6	124	434	First estimation
A.C.	7.8	2.2	16	492	Three weeks follow-up
A.C.	10.1	1.9	178	492	Twelve weeks follow-up
M.C.	9.4	2.2	515	257	First estimation
M.C.		2.2	515	257	Eleven days follow-up
B.F.	9.6	5.2	178	669	First estimation
B.F.	7.7	1.3	124	323	One month follow-up
F.	12.8	3.6	452	911	First estimation
F.		3.2	97	353	Six weeks follow-up
A.M.	5.5	0.1	226	603	First estimation
A.M.	12.8	7.0	226	1029	Three weeks follow-up

Alk. P'tase = Alkaline phosphatase.
A-5-P = 5-nucleotidase.
LDH = Lactic dehydrogenase.
LAP = Leucine aminopeptidase.

creases, the LAP activity ranging from 132 to 1257, with a mean value of 398 units. Mean levels for LDH, alkaline phosphatase and 5-nucleotidase were 377, 11.3 and 2.6 units, respectively. The highest levels in two of these patients (A.M. and H.A.) occurred during the recovery phase when jaundice had markedly decreased. No correlation was observed between the alkaline phosphatase and 5-nucleotidase serum activity, nor was there any relationship between the latter enzyme and the LAP levels. Patients in this group showing marked serum transaminase activity usually had fairly marked elevations of serum LDH; however, some normal LDH values were encountered. Some patients with only moderate transaminase increases showed very marked increases in LDH activity.

Subacute Hepatitis

A group of patients with subacute (alternatively called chronic active hepatitis) were studied. The diagnosis in these cases was confirmed by histological examination of biopsy specimens, and the enzyme levels are shown in Table VI. The activity of all the enzymes was increased in a number of instances. All the patients with LDH levels over 340 units, with one exception (C), were acutely ill. It can be seen that some very high alkaline phosphatase, 5-nucleotidase and LAP values were encountered. The enzyme levels here are similar to those observed in the malignant extrahepatic obstruction group, although in most of these patients jaundice was either moderate or slight. The mean values for the alkaline phosphatase, 5-nucleotidase and LAP activities were 15.6, 5.1 and 859 units, respectively. These values approximated those of the group with carcinoma of the head of the pancreas.

TABLE VI.—SERUM ENZYMES IN SUBACUTE HEPATITIS

Case	Enzymes (units/100 ml.) Alk. P'tase	A-5-P	LDH	LAP	Remarks
J.K.			408	419	
B.A.	18.0	6.0	107	243	Biliary cirrhosis
C.	8.5	1.1	710		
A.C.	9.3	0.4	732	514	
T.	10.4	0.8	650	270	
O.	7.2		608	124	
M.S.	24.0	17.6	340	1514	
M.P.	18.4	4.4	225	1470	
M.	10.5	0.7	288	197	
E.	9.2	1.2	485	704	
J.T.	35.0	3.9	445	1323	
C.B.	20.1	3.4	240	872	Biliary cirrhosis, first estimation
C.B.	31.5	16.3	205	1470	Fourteen months later
J.B.		5.9	43	2426	First estimation
J.B.	32.4	9.4	43	1308	Five-week follow-up
V.	3.1	0.5	178	162	First estimation
V.			89	140	Ten-week follow-up

Alk. P'tase = Alkaline phosphatase.
A-5-P = 5-nucleotidase.
LDH = Lactic dehydrogenase.
LAP = Leucine aminopeptidase.

Portal Cirrhosis and Hepatoma

A number of patients with decompensated portal cirrhosis were studied. All of the patients in this group had clinical evidence of advanced hepatic disease and a history of prolonged alcoholism. In those recorded as having superimposed hepatomas evidence of this change was obtained by biopsy. Enzyme levels for this group are shown in Table VII. The LAP activity was increased in only four instances when there was no malignant change, but in the hepatoma group the enzyme activity was markedly increased. Increases in the serum LDH, 5-nucleotidase and alkaline phosphatase occurred twice as frequently and all these enzymes were markedly increased in the patients with malignant change, with one exception (E). In this case only the LDH and LAP levels were markedly increased. The mean serum alkaline phosphatase, 5-nucleotidase, LDH and LAP activities in the portal cirrhosis series were 12.4, 3.2, 325 and 216 units, respectively, while in those cases complicated by hepatoma formation the mean enzyme activities were 16.4, 4.3, 694.5 and 950.5 units, respectively. Some

TABLE VII.—SERUM ENZYMES IN PORTAL CIRRHOSIS AND HEPATOMA

Case	Enzymes (units/100 ml.) Alk. P'tase	A-5-P	LDH	LAP	Remarks
Cau.			690	86	
Blo.	10.7	3.1	507	180	
Car.	15.1	2.7	406	195	
R.			209	158	
Be.	7.8	2.6	352	58	
L.	12.6		280	119	
F.	13.6		132	201	
W.	10.5		145	162	
Bla.	6.9	0.6	258	203	
Ha.	15.0	0.9	505	367	
Mu.	10.0	3.6	383	73	
Ba.	8.7	0.7	238	73	
Hu.	11.4	16.2	365	125	
D.H.	20.0	3.0	109	698	
A.G.	10.4	1.9	378	203	
M.K.			176	341	
M.M.			335	206	
K.W.	14.3	2.1	280	228	
W.C.	20.0	1.3	147	332	
G.	15.5	5.1	978	1087	Hepatoma
M.C.	20.0	7.1	440	1126	"
E.	12.3	1.1	610	706	"
Co.	18.0	4.0	750	683	"

Alk. P'tase = Alkaline phosphatase
A-5-P = 5-nucleotidase.
LDH = Lactic dehydrogenase.
LAP = Leucine aminopeptidase.

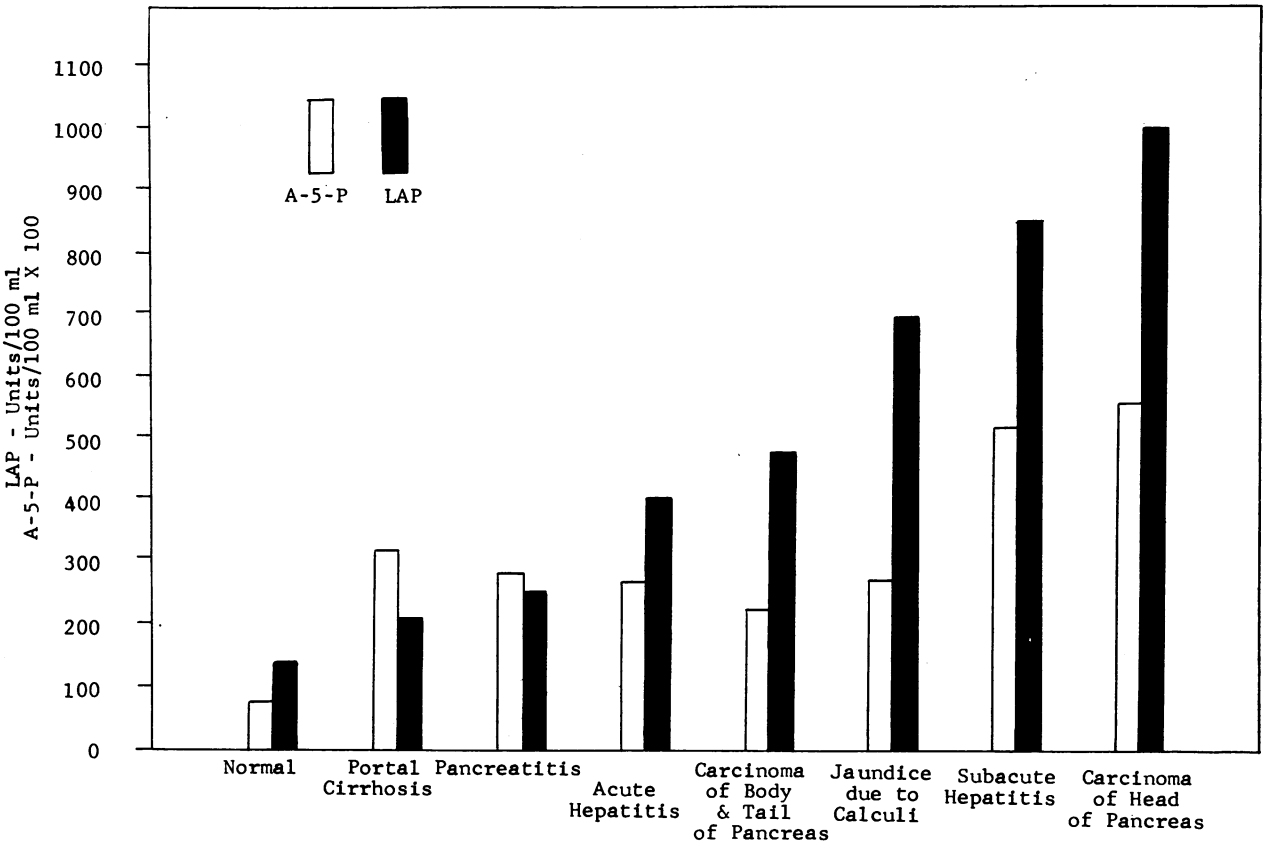

Fig. 1.—Mean serum 5-nucleotidase and leucine aminopeptidase activity.

but not all of the elevated LDH values were associated with moderately increased glutamic oxalacetic transaminase (GO-T) activity. Glutamic pyruvic transaminase (GP-T) activity was rarely increased in this group.

Two patients with obstructive jaundice due to carcinoma of the gallbladder with metastases to liver and pancreas showed only moderate increases in serum LAP. We have observed some striking increases in serum LAP activity in a few instances of non-malignant infiltrations, such as sarcoidosis of the liver and amyloid infiltration.[6] In these cases the other enzymes studied have shown varying and independent abnormalities. Secondary carcinoma, in which the primary was not located in the pancreas or hepatobiliary system, has been associated with a tendency to marked serum LDH activity but a very variable increase in the LAP, 5-nucleotidase and alkaline phosphatase levels. Only rarely did the LAP levels in these patients with secondary liver carcinoma approximate the levels encountered in those with malignancy of the pancreas or hepatoma.

DISCUSSION

Leucine aminopeptidase activity in the serum is markedly affected by extrahepatic obstruction from any cause, and the very high levels encountered in cases of carcinoma of the head of the pancreas reflect mainly the completeness of the obstruction. This is to be expected in view of the relatively large amounts of this enzyme present in bile fluids.[9] However, it appears that infiltration and/or active and progressive disease within the liver also greatly increases serum LAP activity. This is suggested by the high serum leucine aminopeptidase levels frequently encountered in patients with carcinoma of the body of the pancreas and subacute hepatitis. In these two groups the obstructive element was only slight to moderate as judged by the degree of hyperbilirubinemia. The observation that in some instances resolving acute hepatitis is accompanied by rising serum LAP levels suggests that this enzymatic activity is related to the regenerative and healing process. The occurrence of occasional elevations in patients with carcinoma of the pancreas with minimal or no obstructive features and no evidence of metastases suggests that serum LAP activity may be increased by still another mechanism. Monis, Nachlas and Seligman[10] have demonstrated histochemically large amounts of leucine aminopeptidase in the stroma of a number of malignant tumours although the LAP activity of the malignant cells was generally low. These workers believe that LAP activity is intimately associated with fibroblastic proliferation. Burstone[11] has associated the high activity of this proteolytic enzyme in the stroma of tumours with their invasive properties. It would appear from the evidence available that rarely serum LAP may be increased even in the absence of obvious obstruction or metastases and that this may result from

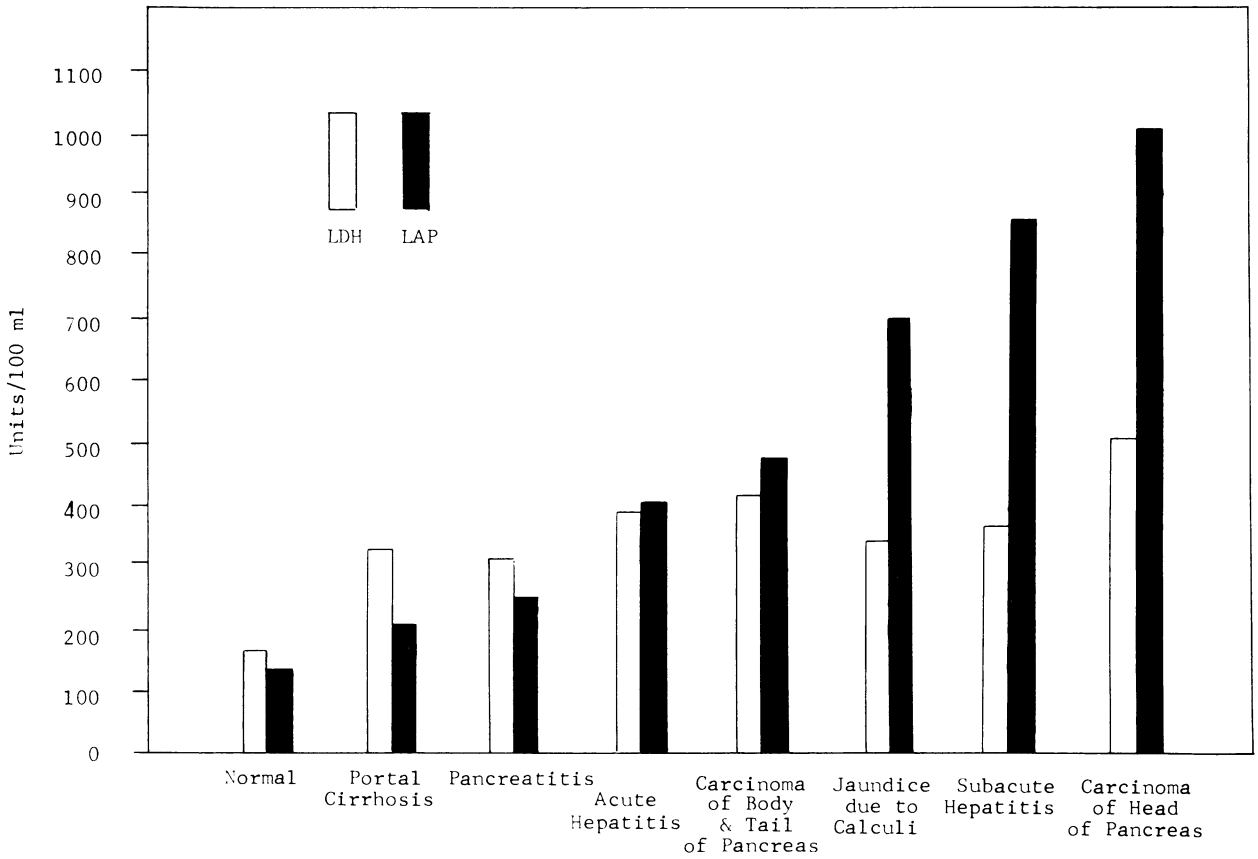

Fig. 2.—Mean serum lactic dehydrogenase and leucine aminopeptidase activity.

abnormal enzyme production within the tumour or within other newly proliferating connective tissue. In this study all the subacute hepatitis patients with one exception (V) showed some cirrhotic changes on microscopic examination of hepatic tissue. High serum LAP levels are commonly encountered in late pregnancy.[4] The occurrence of increased serum LAP levels in some cases of acute pancreatitis may be related to the frequent occurrence of minor degrees of common bile duct obstruction resulting from swelling and edema of the surrounding tissues in this condition. In patients with portal cirrhosis marked increases in serum leucine aminopeptidase activity suggest a superimposed hepatoma.

The occurrence of only slight to moderate elevations of the serum alkaline phosphatase in many of the patients studied here indicates that this enzyme is a much less sensitive indicator of biliary obstruction and intrahepatic disease than is the serum LAP activity. In addition to this lack of sensitivity, this enzymatic estimation has the further disadvantage of being affected by a number of disease states other than those associated with the hepatobiliary system.

The observations on serum 5-nucleotidase activity in this investigation indicate that this enzyme shows much more significant and proportional increases over the normal value than does the serum alkaline phosphatase and has the advantage of being specific for hepatobiliary disturbances, a fact to which reference has previously been made. The 5-nucleotidase activity has been affected in the same diseases that were associated with increased LAP activity. However, elevations of the latter enzyme appear generally to be more striking, and no mathematical correlation exists between the activity of these enzymes. Fig. 1 shows graphically the mean serum 5-nucleotidase and LAP activities, and the independent variation relative to the various diseases investigated is readily seen. The greater mean increases in LAP over 5-nucleotidase activity would appear to indicate that the former enzyme is a more sensitive measure of hepatobiliary disease. However, the estimation of both of these enzymes specific for hepatobiliary disease would appear to be worth-while investigative procedures in evaluating diseases of the liver and biliary tract.

Serum lactic dehydrogenase activity shows variable and usually moderate increases in patients with acute hepatitis. This is to be expected in view of the amount of hepatic cell necrosis present, as evidenced by the marked increases in serum GO and GP transaminase activity. From our data[6] transaminase activity reflects the extent of hepatic cell necrosis in a more sensitive manner than does LDH activity. However, these enzyme alterations are usually brief in cases of acute hepatitis, and prolonged abnormalities usually indicate progression to subacute hepatitis. The variable and often marked elevation of the serum LDH noted in the patients with carcinoma of the pancreas is probably

the effect of the malignancy *per se*. Moore and Wroblewski[1] concluded from their tissue culture data that lactic dehydrogenase is released from malignant cells as a result of altered cell permeability or during mitosis. Riley and Wroblewski[2] have correlated increasing plasma LDH activity with growth of the tumour tissue in transplantable mouse tumours, and Wroblewski[3] has reported increased plasma LDH activity in patients with various types of malignancy. Our observations of increased serum LDH activity in different types of malignancy and the effect of chemotherapy and radiotherapy on this activity are to be published separately. In the cases reported in this study mean LDH activity was almost as high in the group of patients with cancer of the body of the pancreas as it was in those with carcinoma of the head of the pancreas. It would appear, therefore, that obstruction has little effect on the levels of this enzyme. Of the 45 patients with malignancy who had serum LDH estimations prior to surgery or biopsy, 35 had elevated LDH levels. It would appear that, in the absence of primary hepatic or muscle disease, increased plasma LDH is strongly suggestive of malignancy, and from the data in this study elevated serum LDH activity accompanied by marked increases in serum LAP level favours the diagnosis of malignant extrahepatic obstruction. The occurrence of marked increases in serum LDH and LAP activities in a patient with portal cirrhosis suggests the presence of a complicating hepatoma. The mean serum LDH and LAP values for the various groups studied are shown graphically in Fig. 2. The mean serum LDH was highest in the groups with malignancy. The frequent occurrence of increased serum LDH activity noted here indicates that the measurement of this enzyme in the blood is a useful adjunct to the diagnosis of malignancy involving the hepatobiliary system.

SUMMARY AND CONCLUSIONS

Serum alkaline phosphatase, 5-nucleotidase, lactic dehydrogenase and leucine aminopeptidase activities have been investigated in patients with a number of conditions affecting the hepatobiliary system, and the mechanism whereby alterations in these enzymes occur has been discussed.

Leucine aminopeptidase activity is a sensitive indicator of biliary obstruction; serum 5-nucleotidase is somewhat less sensitive.

Leucine aminopeptidase and 5-nucleotidase activities are increased by malignant infiltration of the liver and primary hepatic disease even in the absence of jaundice.

Serum lactic dehydrogenase is increased frequently in primary hepatic disease and in malignant states but is not increased by bile duct obstruction *per se*.

Elevated serum leucine aminopeptidase and lactic dehydrogenase levels in a patient with obstructive jaundice suggests a malignant etiology.

In the anicteric patient elevated leucine aminopeptidase and lactic dehydrogenase levels suggest malignant infiltration of the liver or chronic and progressive hepatic disease.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

INSANITY AND ITS RELATION TO THE STATE

In view of the increasing amount of interest taken by the public in all matters affecting its general welfare, it might hardly seem necessary to advance a special plea for the granting of opportunities for study and investigation to those whose chief interest is to ascertain the surest and best means of promoting rational thought and action.

Much money is spent on our army and navy and munitions of war, and probably rightly so in the present state of affairs, in order to maintain the independence of our country. But would it not be equally foreseeing in this age in which a struggle has begun, a struggle in which science and brains are to take the place of sword and sinews, to organize some concerted and well-directed effort to find out the most efficacious way of increasing the brain power of the nation?

Much money has been spent by a munificent government in investigating conditions about the North Pole, but how much has been devoted to the study and investigation of the causes and prevention of the insanities, a question in which, as I hope to be able to show, we might be much more vitally interested, first from a purely humanitarian point of view, and secondly from the point of view of dollars and cents.

Let us consider this question from the humanitarian viewpoint. At present, in the wealthy city of Montreal, and in the province of Quebec, we have absolutely no place where patients suffering from deranged mental mechanism, it matters not what may have been its cause, or however slight its nature, we have no place, I say, where such patients can be admitted and receive scientific study and investigation and rational treatment. Our great general hospitals, well equipped as they are in all other lines, have absolutely no conveniences for this great class of sufferers. They refuse to admit them, and one cannot blame them altogether. The other patients must be considered; but is it fair that this great class of patients should be absolutely neglected? . . .

Disorders of metabolism, derangement of the heart's function or that of the kidneys were more easy to study, and it is only in the last few years that any success has crowned the efforts which have been made to understand the causes and the manner of development of disorders of that most important of all functions of our human mechanism, the mind.—Colin K. Russel: *Canad. Med. Ass. J.*, 3: 771, 1913.