2) Such change in distribution of hepatic blood flow as this may bring out the insufficient nutritional supply for the whole body, though it compensates the supposed anoxic conditions of the liver cells due to the decreased blood flow.

3) This change in distribution and other hemodynamic conditions tend to accelerate the production of ascites, but if it is produced, it is able to transfer rapidly into the systemic circu-

lation in the experimental pulmonary hypertension.

4) In congestive heart failure of man, ascites transfers rapidly from peritoneal cavity to systemic circulation, and this rapid transfer of ascites is thought to compensate the decreased hepatic blood flow, though this compensatory mechanism tends to fail if right ~~heart~~ failure is far advanced.

heart

3. Liver Function Tests in Congestive Heart Failure with Special Reference to Enzymatic Activities[†]

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IT IS REPORTED by Chavez that one of the organs that suffer most in heart failure is undoubtedly the liver. Hepatic disturbances in cases of congestive heart failure have been studied on the basis of liver function tests including BSP, bilirubin excretion and colloidal reaction as well as of histological findings of hepatic tissue. But few reports seem to have been made of an enzymatic approach.

In the present study cases of congestive heart failure were subjected to various liver function tests and additionally by enzymatic tests, in an attempt to pursue the hepatic disturbances developed. Chronological observations were made of the constrictive pericarditis experimentally induced in rabbits as to the animal's hepatic function with an emphasis on enzymatic activities of serum and hepatic tissue in reference to histological findings.

CLINICAL OBSERVATIONS

Material:

Those observed during April 1962 and March 1963 were 96 cases of congestive heart failure consisting of 28 males and 68 females of 15-79 years of age. The causative diseases for congestive heart failure were 39 cases of rheumatic heart disease, 19 cases of arteriosclerotic heart disease, 13 cases of rheumatoid valvular disease, 9 cases of chronic cor pulmonale, 7 cases of syphilitic heart disease, 5 cases of hypertensive

heart disease and 4 cases of endocrine heart disease.

The severity of the above cases was classified by the New York Heart Association standards (NYHA). The cases were divided on the basis of onset into two categories, acute failure which referred to a rapid progress during the two weeks prior to the present study and chronic failure which showed no progress during the same period. The acute category included cases with initial onset and those with acute ~~exacerbation~~ of previously controlled failure. The present cases were divided into a right sided group, a left sided group and a combined group on the basis of venous pressure and clinical findings. Liver function tests and serum enzymatic activity tests were performed (**Table I**).

Clinical Symptoms:

The incidence of hepatomegaly, splenomegaly, pleural effusion, ascites, edema, elevated venous pressure and a prolonged circulation time observed in the cases belonged mostly to IV stage, according to NYHA. The above incidence was also observed in high percentage in an acute failure group as well as in a combined group (**Table II**).

Liver Function in Cases of Congestive Heart Failure:

The results of the tests were analysed in terms

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TABLE I NORMAL RANGE FOR LIVER FUNCTION TESTS AND SERUM ENZYMATIC ACTIVITIES

Function	Tests	Normal Range
Bilirubin Excretion	Serum Bilirubin	Total
		Direct
		Indirect
	Urine Bilirubin	(-)
	Urine Urobilinogen	(±)
Dye Excretion	BSP (45')	0 — 3%
Protein Metabolism	Total Protein	6.3 — 7.9 g/dl
	Albumin	55.4—65.2%
	Globulin	34.7—44.6%
	α ₁	3.4 — 4.1%
	α ₂	6.7 — 7.8%
	β	9.8 — 11.8%
	γ	14.1—21.7%
	A/G	1.2 — 1.8%
	Colloidal Reaction	
	CCF	(-)-(+)
	TTT	0—4
Carbohydrate Metabolism	Kunkel	12 u ↓
	Cobalt Reaction	R ₃ —R ₄
	Galactose Tolerance Test	2 g ↓
	Fasting Blood Sugar	70—100 mg/dl
Lipid Metabolism	Serum Cholesterol	150—260 mg/dl
	Ester Ratio	60—75%
Detoxication	Hippuric Acid Synthesis	0.7 g ↑
Enzymatic Activity	Alkaline Phosphatase (ALP)	2—5 u
	Acid Phosphatase (Acid-P)	0.8 u ↓
	Cholinesterase (ChE)	0.5 — 0.8 ΔPH
	GOT	8 — 40 u
	GPT	5 — 35 u
	Glucose-6-phosphatase (G6P)	0 — 6 u
	Phosphohexose Isomerase (PHI)	8 — 40 u
	Aldolase (ALD)	2 — 9.6 u
	Lactic Dehydrogenase (LDH)	100—600 u

TABLE II CLINICAL FINDINGS OF CLASSIFIED GROUPS

Clinical Findings	Groups								
	NYHA Standards				Status of Development		Involved Site		
	IV	III	II	I	Acute	Chronic	R-Sided	L-Sided	Combined
Hepatomegaly, %	78.5 (1.9 f.b)	83.5 (2.1 f.b)	73.5 (1.4 f.b.)	60.0 (0.6 f.b)	76.4 (1.5 f.b)	72.0 (1.5 f.b)	58.0 (1.3 f.b)	64.0 (0.8 f.b)	88.8 (2.0 f.b)
Splenomegaly, %	3.0	0	0	0	0	1.4	0	0	2.0
Pleural Effusion, %	11.4	0	0	0	12.0	1.3	0	0	8.0
Ascites, %	15.3	0	0	0	16.0	1.4	0	4	8.5
Peripheral Edema, %	85.0	54.5	33.3	0	88.5	42.8	47.0	45.8	63.0
Venous Pressure, mmH ₂ O	195.2	168.3	162.1	100.0	179.3	160.8	161.7	126.6	188.1
Circulation Time	Ether, sec	13.5	13.0	10.4	7.8	13.8	11.5	13.9	10.7
	Dechychol, sec	29.9	24.5	25.3	17.7	27.8	23.6	25.8	21.2
									27.7

of the severity, development and involved site of congestive heart failure. Liver function tests and serum enzymatic activity tests were performed for the four groups classified by NYHA (Fig. 1, 2). As a result it was demonstrated that the severer cases, the more increase in direct

bilirubin and urobilinogen and the more retention of BSP, the more decrease in detoxication and the more increase in serum glucose-6-phosphatase (G6P), aldolase (ALD) and lactic dehydrogenase (LDH). Liver function tests and serum enzymatic activity tests were performed

Fig. 1. Liver function tests and serum enzymatic activities in terms of severity classified by the NYHA standards (I).

Fig. 2. Liver function tests and serum enzymatic activities in terms of severity classified by the NYHA standards (II).

for the two groups of congestive heart failure, an acute group and a chronic group. The acute group showed an increase in γ -globulin, a retention of BSP, a decrease in detoxication, and an increase in alkaline phosphatase (ALP), GOT, G6P, phosphohexose isomerase (PHI), ALD and LDH. The chronic group showed a slight increase in direct bilirubin, a retention in BSP a decrease in detoxication and an increase in ALD and LDH. The acute group disclosed poorer results of liver function and of serum enzymatic activity than the chronic group. The liver function tests and serum enzymatic acti-

vity tests performed for involvement revealed that a right sided group showed a retention of BSP and an increase in γ -globulin; a left sided group showed a retention of BSP, a decrease in detoxication and an increase in G6P, ALD and LDH; a combined group showed a retention of BSP, a decrease in serum protein, a decreased detoxication, and an increase in ALP and LDH. The above results revealed that liver dysfunction in cases of congestive heart failure was observed rather markedly in a NYHA IV stage group, an acute heart failure group, and a combined heart failure group. The result of test in

cases of congestive heart failure was the worst in detoxication, followed by LDH activity, BSP, ALD activity, carbohydrate metabolism, ALP and cholinesterase (ChE) in descending order. The result of the above examinations are considered to reflect liver function in cases of congestive heart failure.

A Comparative Study of Serum Enzymatic Activities and Liver Function in Cases of Congestive Heart Failure, Chronic Cor Pulmonale and Hepatic Disease:

A comparative study of the results of serum enzymatic activities in cases of congestive heart failure, chronic cor pulmonale and hepatitis revealed that the last cases showed a marked increase in transaminase and in glycolytic enzymes over the other two cases. Even cases of acute congestive heart failure which show the most marked changes in enzymatic activities of the cases of congestive heart failure revealed apparently less destruction of liver cells and less metabolic disturbances than cases of hepatitis. Cases of chronic cor pulmonale showed much less changes in enzymatic activities than cases of acute congestive heart failure. The poorest results of BSP and detoxication were revealed by cases of hepatitis, followed by cases of acute congestive heart failure and cases of cor pulmonale in order.

The Clinical Course of Congestive Heart Failure in Reference to Changes of Liver Function Test:

An attempt was made to study which of the changes in liver function might be responsible

for the improvement or deterioration in cases of congestive heart failure. As a result it was disclosed that the changes in detoxication, BSP and LDH were most markedly reflected on the clinical course, followed by ChE, bilirubin, PHI and ALD in order. Thus the changes in enzymatic activities were well reflected on those in the clinical course. Even cases of congestive heart failure showing an apparent improvement of liver function tests and clinical findings were subjected to a subsequent deterioration so long as they maintained an increase in enzymatic activities.

EXPERIMENTAL OBSERVATIONS

Eighty-nine rabbits weighing about 3 kg were employed. Introduction of talcum powder and slices of sponge into the pericardium of the animals resulted in constrictive pericarditis which was complicated with congestive heart failure following the intake of salt and the loading with physical exertion. These animals were observed for 112 days after the treatment, as to serum bilirubin, protein fraction, colloidal reactions, ALP, acid phosphatase (Acid P), ChE, GOT, GPT, G6P, ALD, PHI and LDH activities. In the meantime studies were made of enzymatic activities in the serum, liver tissue and myocardium, in reference to histological findings of liver tissue. No correlation was observed between the symptomatic manifestations of the animals and the changes in bilirubin, protein fraction, colloidal reactions.

Change in Serum Enzymatic Activities in Rabbits with Congestive Heart Failure due

TABLE III CHRONOLOGICAL CHANGES OF ENZYMATIC ACTIVITIES IN RABBITS WITH EXPERIMENTAL CONSTRICTIVE PERICARDITIS

Enzyme	Days											
	5	7	10	14	21	28	42	56	70	84	112	Normal
ALP u	6.6	5.0	4.3	3.5	4.3	6.6	4.0	3.6	3.6	3.5	4.0	5.4
Acid-P u	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.1	2.2	2.5
ChE u	0.12	.0	0.12	0.11	0.06	0.14	0.77	0.19	0.16	0	0	0.10
GOT u	113.0	52.0	51.0	62.0	34.0	47.0	22.0	43.0	39.0	23.0	46.0	80.0
GPT u	67.0	32.0	42.0	43.0	32.0	30.0	39.0	30.0	23.0	31.0	41.0	41.0
G6P u	52.0	273.0	179.0	23.0	0	0	0	8.0	11.0	0	0	0
PHI u	189.0	266.0	207.0	100.0	65.0	64.0	51.0	46.0	56.0	54.0	63.0	54.0
ALD u	78.0	131.0	101.0	98.0	56.0	63.0	48.0	73.0	70.0	50.0	63.0	59.0
LDH u	1773.0	3550.0	3010.0	2900.0	2740.0	1007.0	840.0	757.0	1173.0	1467.0	1580.0	600.0

Fig. 3. Chronological changes of enzymatic activities in rabbits with experimental constrictive pericarditis.

to Experimental Constrictive Pericarditis:

In the study of the activities of nine kinds of serum enzyme, those glycolytic enzymes and transaminase which were closely related with a morbid course of congestive heart failure were pursued with the following results (Table III, Fig. 3). Seven to ten days after the treatment

G6P, PHI, ALD and LDH showed an increase in enzymatic activities. On the 21st day after the treatment G6P, PHI and ALD showed a decrease in enzymatic activities to the pretreatment stage; LDH showed a slightly delayed recovery. About 70 days after the treatment G6P showed a slight increase of enzymatic activities which, however, was the highest of LDH, ALD and PHI in order.

Serum Enzymatic Activities Studied in Comparison with Enzymatic Activities in Liver Tissue and Myocardium:

Determination was made of the activities of four kinds of glycolytic enzyme in the serum, the liver tissue and the myocardium. An increase or decrease against a normal value of the activity in the determination was presented in percentage. The serum showed an increase 7–10 days and about 70 days after the treatment, when liver tissue and the myocardium showed a decrease in the activity, but the above increase and decrease showed no exact mirror image relationship (Table IV, Fig. 4).

The Enzymatic Activities of the Serum and Liver Tissue Studied in Reference to Histological Findings of the Liver:

Seven to ten days after the treatment the findings of liver tissue revealed an enlargement of the central vein and sinusoid, a hemorrhage in the central lobule, an atrophy and necrosis of liver cells (Fig. 5). Simultaneously there were found an increase in serum enzymatic activities and a decrease in them of liver tissue and the

TABLE IV CHRONOLOGICAL CHANGES OF ENZYMATIC ACTIVITIES IN SERUM LIVER AND MYOCARDIUM

Enzyme		Days										
		5	7	10	14	21	28	42	56	70	84	112
G6P	Blood %	+7900	+54100	+26200	+2300	0	0	0	+800	+1600	0	0
	Liver %	-45.1	-54.1	-18.4	-7.2	-5.0	0	-0.7	-11.2	-14.4	0	0
PHI	Blood %	+250.0	+374.1	+264.8	+85.2	+19.8	+18.5	0	0	+4.3	0	+16.3
	Liver %	-17.1	-22.6	-24.9	-8.5	-6.6	-2.2	0	-0.9	-21.4	-0.6	-9.8
Myocardium %		-11.1	-21.6	-20.9	-8.9	-0.9	-2.5	0	-0.4	-21.0	0	-7.2
ALD	Blood %	+89.8	+130.5	+93.2	+66.1	0	+6.8	+3.4	+6.8	+22.0	+18.6	+6.8
	Liver %	-23.8	-37.8	-28.5	-19.7	0	-7.6	0	-18.7	-22.1	-20.5	-4.4
Myocardium %		-16.3	-36.6	-23.8	-31.7	-8.9	-28.9	-18.9	-1.2	-20.1	-18.9	-18.3
LDH	Blood %	+195.5	+491.7	+401.7	+383.3	+356.7	+67.8	+40	+26.2	+95.5	+144.5	+163.3
	Liver %	-32.6	-66.5	-62.2	-59.7	-58.5	-25.4	-3.1	-3.5	-5.8	-51.0	-91.2
Myocardium %		-31.3	-64.8	-59.0	-51.1	-42.3	-12.0	-3.6	-7.6	-16.4	-19.9	-20.8

Fig. 4. Chronological changes of enzymatic activities in serum and liver.

myocardium. Twenty-eight to forty-two days after the treatment, an enlargement of the sinusoid and a vacuolization of the central lobule were observed with an almost complete recovery of enzymatic activities in the serum and liver tissue. Seventy to a hundred days after the treatment a marked vacuolization was observed in liver cells; some rabbits showed a hemorrhage in the lobule and necrosis in liver cells. At this period a trend of increase in enzymatic activities was observed in the serum. The present observation period, being 112 days, did not seem long enough to cover a developmental course of congestive liver cirrhosis. A longer observation period is being contemplated to pursue a whole course of the disease.

SUMMARY

Clinical and experimental studies were made of hepatic disturbances complicated with congestive heart failure in 96 human cases and in 89 rabbits with congestive heart failure of induced constrictive pericarditis origin.

Fig. 5. Histological findings of the liver tissue of experimental constrictive pericarditis rabbits.

Dilatation of central vein and sinusoid, hemorrhage and necrosis of central lobules occurring 7 days after treatment.

Hepatic disturbances were severe in NYHA IV stage cases, acute cases and combined cases. Cases of congestive heart failure with hepatic disturbances were mainly featured by increased activities in LDH, PHI and ALD as well as by a deterioration. A chronological study of the enzymatic activities of the serum, liver and myocardium, liver function tests and histological examinations of liver tissue in experimental pericarditis rabbits revealed that the serum enzymatic activities showed a good correspondence to clinical and histological findings. An increase in the activities of the glycolytic enzymes studied seemed to be due to anoxia in liver cells and an increased venous pressure resulting in a mechanical compression of liver cells leading to a destruction or disturbed cell metabolism by which glycolytic enzymes were released in the blood. In testing liver function the methods so far employed have been performed only in terms of residual function. Since the liver is an organ which is ready for compensatory function, when liver cells are partially impaired, some liver function may remain normal on test in the presence of hepatic disturbances. Besides routine methods, a stress was given to the importance of enzymatic activities which reflect a destruction and metabolic disturbances of liver cells in cases of congestive heart failure; a study was also made of rabbits with experimental constrictive pericarditis.

Co-workers : Dr. Yasuko Siozaki and Dr. Fukiko Takahashi.

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4. Discussion[†]

CHAIRMAN: Dr. Inoue and Dr. Yorifuji! I would like to ask you to discuss the hypoxemia or anoxia in the congestive heart failure.

Dr. INOUE: The problem of the anoxia in congestive heart failure must be studied by long continued observations. Our subjects on observation were not examined under these conditions, but the diminishing cardiac output, the diminishing hepatic blood flow and the low arterial oxygen content by catheterization studies were obtained.

The splanchnic oxygen consumption, in our moderate cases with heart failure, maintains a normal by an increased arterial-hepatic venous oxygen difference. But, we found that in severe cases the consumption is clearly decreased, and then the liver cells received a blood with lower oxygen tension.

Dr. YORIFUJI: Before I discuss the problem in question, I would like to talk that the hepatic function is generally not so severely disturbed in congestive heart failure as one expects. My experiments intended to show what that is. As one know, liver is supplied its blood from two vessels, i. e. hepatic artery and portal vein, and these two vessels stand in compensatory relations. As far as my experiments showed, when pulmonary hypertension occurred in right heart failure, associated with the decreased hepatic flow, the hepatic arterial flow relatively increased. Hepatic artery is rich in oxygen. Therefore, anoxia of hepatic cells due to decreased hepatic flow is compensated by the distributional change. This is the reason why liver is relatively good

in function even when congestive heart failure is advanced. Regarding the mechanism of central necrosis of the liver, I would like to inform that it is less likely to occur from the anoxia, and I think that is due to the increased central venous pressure.

CHAIRMAN: Hepatic vein catheterization seems very difficult, especially in cases of congestive heart failure. Let me ask Dr. Inoue if he has anything to comment on Dr. Yorifuji's speech.

Dr. INOUE: There may be some differences in hemodynamics in the anoxic state between the acute and chronic congestive heart failure. In the acute heart failure, there may be observed the increase in cardiac output or hepatic blood flow; regarding to this point, I am agreeable to Dr. Yorifuji's speech.

CHAIRMAN: So far, hypoxemia seems to have been considered as a main causative factor. But Dr. Inoue and Dr. Yorifuji's opinions seem to imply that a low hepatic flow constitutes another factor.

Dr. YORIFUJI: I would like to remark that anoxia, low blood flow and changes in venous pressure or sinusoid pressure are correlated in the congestive heart failure.

CHAIRMAN: Dr. Inoue and Dr. Sameshima are requested to discuss on the cases of hepatic cirrhosis due to congestive heart failure and related cases.

Dr. SAMESHIMA: The liver biopsy on cases of persistent congestive heart failure revealed mostly liver fibrosis and rather a few liver cir-

[†] This discussion was arranged by Editorial Secretary (K. Ogino M.D.).